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References: Chem. Abstr. 124:164848
Chem. Abstr. 131:27828
Derwent 1989-197892/26

The following information is taken from the documents submitted by the applicant

A request for examination is made under §44 of the Patent Law

Use of substances which increase the intracellular content of cyclic adenosine monophosphate (cAMP) or stimulate the activity of cAMP-binding proteins, for the treatment of diseases of the bladder.

The invention involves the use of substances which increase the intracellular concentration of cAMP or stimulate the functional activity of cAMP-binding proteins by direct stimulation of adenylate cyclase activity, association with beta-receptors and inhibition of types 1, 2, 3, 4, 7 and 8, for the treatment of disorders of the storage function of the bladder (urgency symptoms, urge incontinence, pollakiuria, nycturia and instabilities of the detrusor muscle).

Such substances are, for example: forskolin (7-acetoxy-1a,6ß,9a-trihydroxy-8,13-epoxy-14-en-11-one), L-858051 (7-deacetyl-7-(N-methylpiperazino)-butyryl forskolin), adenylate cyclase toxin, xamoterol, denopamine, clenbuterol, procaterol, salbutamol, sameterol, formoterol, terbutaline, fenoterol, BRL 37344, ZD 7114, CPG 12177, CL 316243, ICI 215,001, pindolol, isobutylmethyl xanthine (IBMX), methoxymethyl-IBMX, vinpocetine, vincamine, HA-588, calmodulin antagonists, EHNA (erythro-9-(2-hydroxy-3-nonyl) adenine), amrinone, cilostamide (OPC 3698), enoximone, milrinone, quazinone (Ro 13-6438), siguazodan, trequinsin (HL 725), 8-Br-cGMP, 8-pCPT-cGMP, Sp-8-Br-cGMPS, PET-cGMP, CD-80,633, denbufylline (BRL 30892), etazolate (SQ 20009), 3-ethyl-1-(4-fluorophenyl)-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolopyridine, rolipram (ZK 62711), Ro 20-1724, RP 73401, RS 25344, SB 2074499, TVX 2706, zardaverine, 8-bromine-cAMP (8-bromoadenosine-3',5'-cyclic monophosphate), Sp-cAMPs ...

Specification

The basis of the patent is our own scientific work from which the use of pharmacological substances which increase the intracellular concentrations of cyclic adenosine monophosphate by various mechanisms and the use of structural analogs of cAMP which stimulate cAMP-binding proteins can be derived for the treatment of disorders of the storage function of the bladder.

General

Disorders of the storage function of the bladder due to over-activity of the detrusor muscle are a widespread disease in industrialized Western nations; its prevalence is between 33 and 61% in people over 65 years of age. Pharmacotherapy is today the most important clinical option for treating urgent urination symptoms and urge incontinence. The central problem is the elimination of the over-activity of the detrusor without an adverse effect on normal miction or other bodily functions. Since the contractility of the detrusor is induced by the stimulation of muscarine receptors by the binding of cholinergic transmitter molecules such as acetylcholine, substituted tertiary and quaternary amine compounds from the group of anticholinergics (trospium chloride, oxybutynin, tolterodine) are used above all. The clinical use of these preparations is, however, limited by their low bioavailability and the typical anticholinergic side effects.

The tonicity of a smooth-muscle organ depends on the intracellular concentration of the cyclic nucleotide monophosphates cAMP and cGMP. This concentration is regulated by an equilibrium of synthesis by cellular adenylate and guanylate cyclases and degradation by hydrolyzing phosphodiesterases. Stimulation of the cellular concentrations of cAMP and cGMP by suitable substances can result in relaxation of a smooth-muscle tissue. This mechanism has been described by C.D. Nicholson, R.A. Challis and M. Shahid (Pulm. Pharmacol, 7:1-17, 1994) and by T.J. Trophy et al. (J. Pharmacol. Exp. Ther. 265:1213-1223, 1993). Primary receptors of cAMP are cellular protein kinases, the phosphorylating activity of which is activated by the binding of the cyclic nucleotide. The substrates of the cAMP-dependent protein kinases are ion channels and ATPases of the sarcoplasmic reticulum and cell membrane, the phosphorylation of which leads to a efflux of Ca^{2+} from the cytosolic compartment and thus to relaxation of the smooth musculature. Stimulation of the cAMP content or the phosphorylating activity of cAMP-binding protein kinases in the detrusor musculature by

the substances hereinafter described should effectively improve the symptoms of urinary incontinence and be superior to the established pharmacological treatment methods due to a better ratio of effect on the target organ to side effects.

Our own work which is the basis of the claim

The following results of our own scientific work show a physiological dominance of the cAMP-dependent signal transmission paths in the regulation of the contractile activity of the human bladder:

The detection of the hydrolytic activity of the cAMP-hydrolyzing PDE isoenzymes 1, 2, 3 and 4 in the human detrusor musculature (Fig 1).

The relaxing effect of the adenylate cyclase stimulator forskolin and different inhibitors of cAMP-hydrolyzing PDEs on the muscarinergic tension of isolated strip preparations of human detrusor musculature (Fig. 2)

The relaxing effect of the cAMP structural analogs Sp-8-cAMP and DCI-cBIMPS on the muscarinergic tension of isolated strip preparations of human detrusor musculature (Fig. 3)

The stimulation of the intracellular cAMP concentration of isolated human detrusor musculature by forskolin and inhibitors of cAMP-hydrolyzing PDEs (Figs. 4, 5 and 6)

Claims

1. The use of pharmacological substances which stimulate the activity of cellular adenylate cyclases and thus increase the intracellular cAMP concentration, for the treatment of urgent urination symptoms, urge incontinence, pollakiuria, nycturia and instabilities of the detrusor muscle. Such substances are for example: forskolin (7ß-acetoxy-1a,6ß,9a-trihydroxy-8,13-epoxy-14-en-11-one). L-858051 (7-deacetyl-7ß-(N-methyl piperazino)-butyryl forskolin) and adenylate cyclase toxin.

2. The use of pharmacological substances which stimulate the activity of the adenylate cyclase associated with these receptors by binding to $ß_1$, $ß_2$ and $ß_3$ adrenoreceptors of the bladder musculature, for the treatment of urgent urination symptoms, urge incontinence, pollakiuria, nycturia and instabilities of the detrusor muscle. Such substances are for example, xamoterol, denopamine, clenbuterol, procaterol, salbutamol, sameterol, formoterol, terbutaline, fenoterol, BRL 37344, ZD 7114, CPG 12177, CL 316243, ICI 215,001 and pindolol.

3. The use of pharmacological substances which inhibit the activity of cellular cAMP-hydrolyzing phosphodiesterases and thus increase the intracellular cAMP concentration, for the treatment of urgent urination symptoms, urge incontinence, pollakiuria, nycturia and instabilities of the detrusor muscle. Such substances include: PDE1 inhibitors such as isobutylmethyl xanthine (IBMX), methoxymethyl-IBMX, vinpocetine, vincamine, HA-588 and calmodulin antagonists, PDE2 inhibitors such as EHNA (erythro-9-(2-hydroxy-3-nonyl) adenine), PDE3 inhibitors such as amrinone, cilostamide (OPC 3698), enoximone, milrinone, quazinone (Ro 13-6438), siguazodan,

trequinsin (HL 725), 8-Br-cGMP, 8-pCPT-cGMP, Sp-8-Br-cGMPS, PET-cGMP and inhibitors of PDEs 4, 7 and 8 such as CD-80,633, denbufylline (BRL 30892), etazolate (SQ 20009), 3-ethyl-1-(4-fluorophenyl)-6-phenyl-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolopyridine, rolipram (ZK 62711), Ro 20-1724, RP 73401, RS 25344, SB 2074499, TVX 2706 and zardaverine.

4. The use of pharmacological preparations of structural analogs of cyclic adenosine monophosphate (cAMP) which stimulate the phosphorylating activity of cellular cAMP-binding protein kinases and thus reduce the cytosolic concentration of free Ca^{2+}, for the treatment of urgent urination symptoms, urge incontinence, pollakiuria, nycturia and instabilities of the detrusor muscle. Such substances are for example: 8-bromine-cAMP (8-bromoadenosine-3',5'-cyclic monophosphate), Sp-cAMPS (Sp-adenosine-3',5'-cyclic monophosphorothioate), Sp-8-Cl-cAMPS, 8-CPTc-cAMP (8-(4-chlorophenylthio)-adenosine-3',5'-cyclic monophosphate) and Sp-5,6-DCl-cBIMPS (Sp-5,6-dichloro-1-ß-D-ribofuranosyl-benzimidazole-3',5'-monophosphothioate).

5. Any combination of the pharmacological preparations cited under 1, 2 and 3.

Four pages of diagrams follow

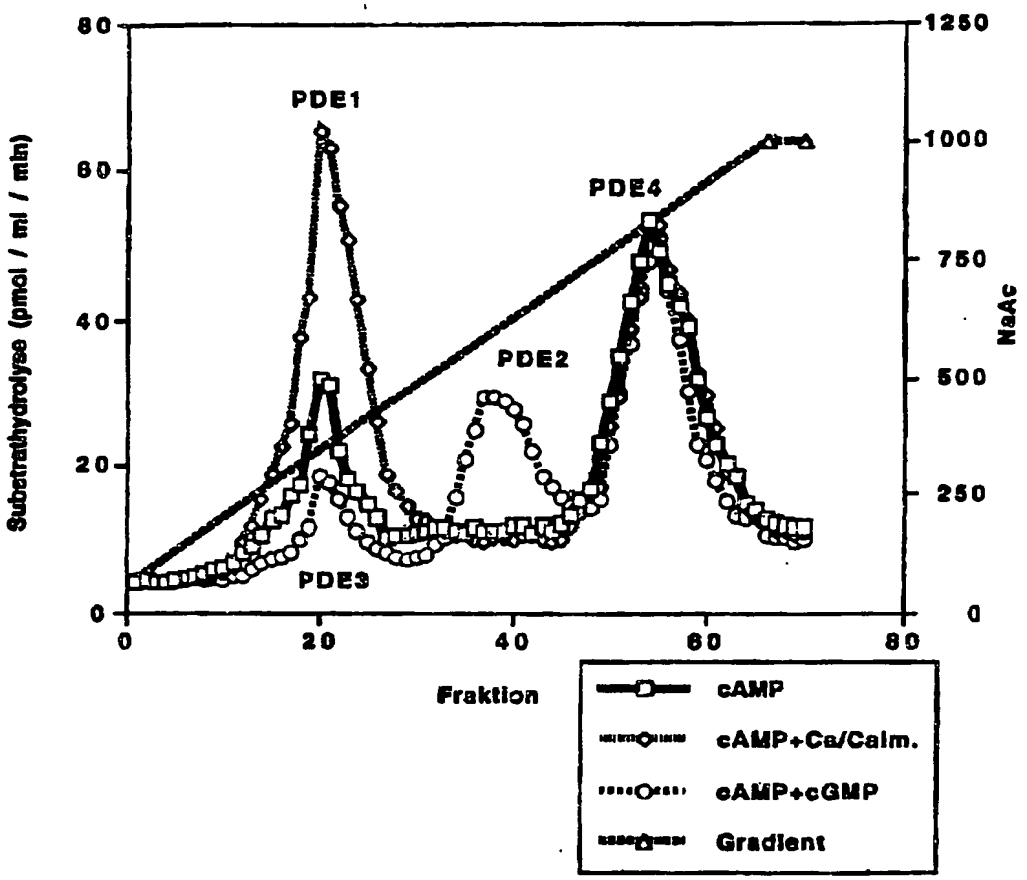

Fig. 1: Detection of the activity of the cAMP-hydrolyzing PDEs 1, 2, 3 and 4 in a cytosolic 42,000 g supernatant of a tissue homogenate of human detrusor musculature.

Key: Substrathydrolyse = substrate hydrolysis; Fraktion = fraction

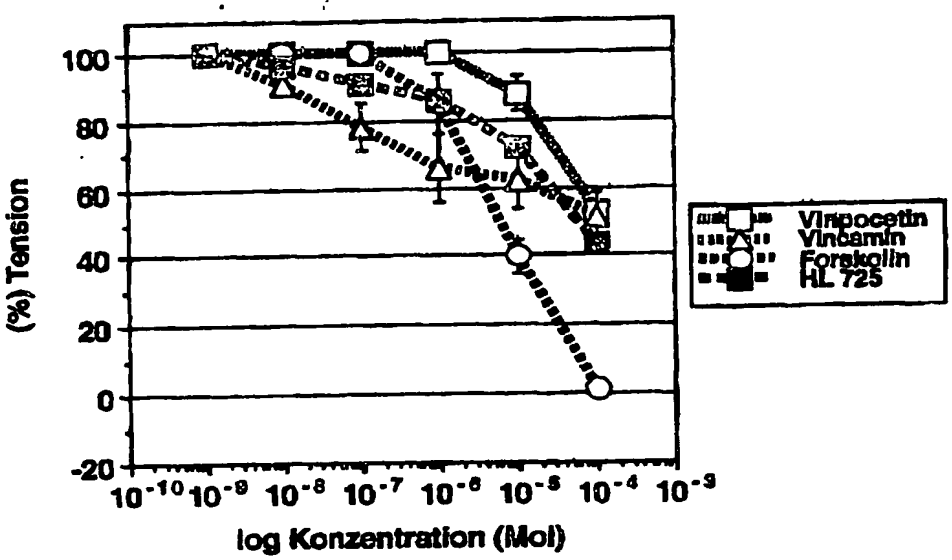

Fig. 2: Relaxing effects of the adenylate cyclase activator forskolin and some inhibitors of cAMP-hydrolyzing PDEs on the muscarinergic tension of isolated strip preparations of human detrusor musculature

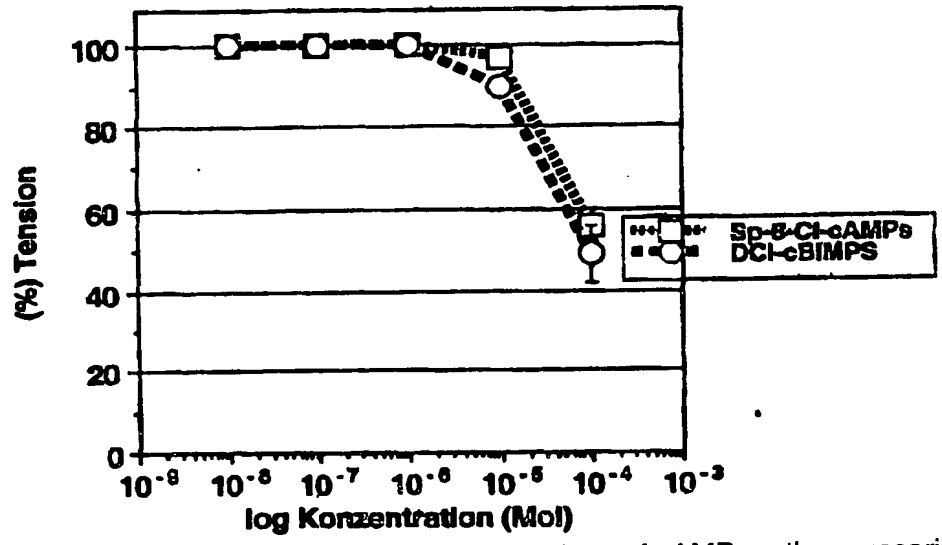

Fig. 3: Relaxing effects of two structural analogs of cAMP on the muscarinergic tension of isolated strip preparations of human detrusor musculature

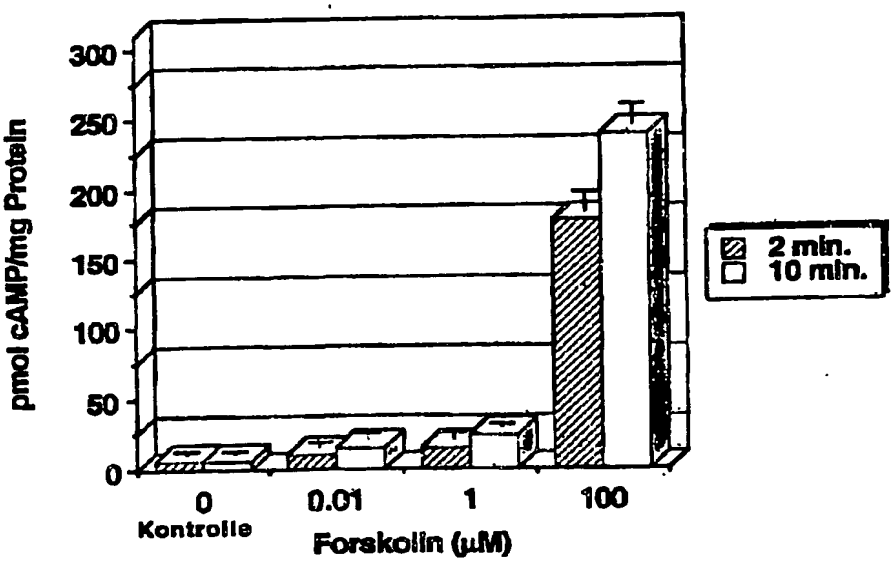

Fig. 4: Stimulating effects of different concentrations of the adenylate cyclase activator forskolin on the tissue content of cAMP in strip preparations of isolated human detrusor musculature

Key: Kontrolle = control

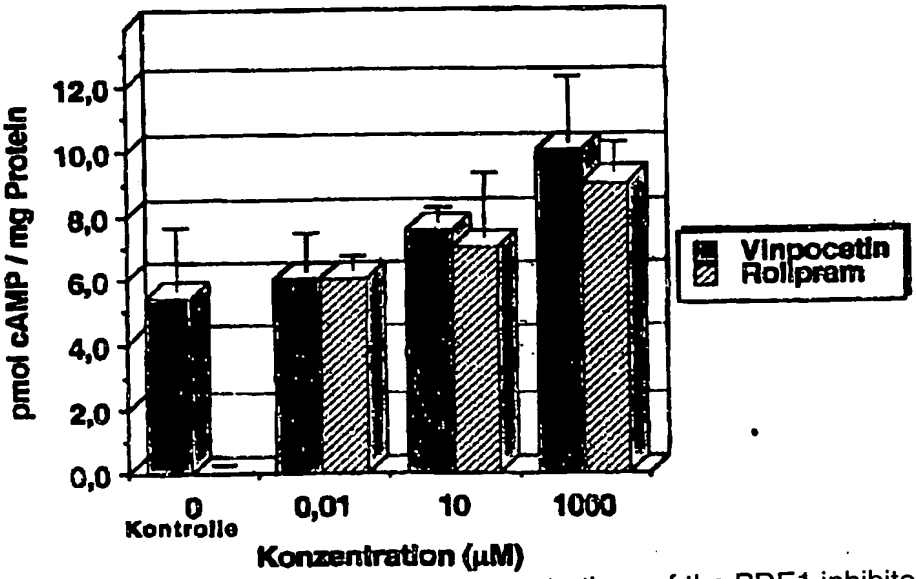

Fig. 5: Stimulating effects of different concentrations of the PDE1 inhibitor vinpocetine and the PDE4 inhibitor rolipram on the tissue content of cAMP in strip preparations of isolated human detrusor musculature

Key: Kontrolle = control; Konzentration = concentration

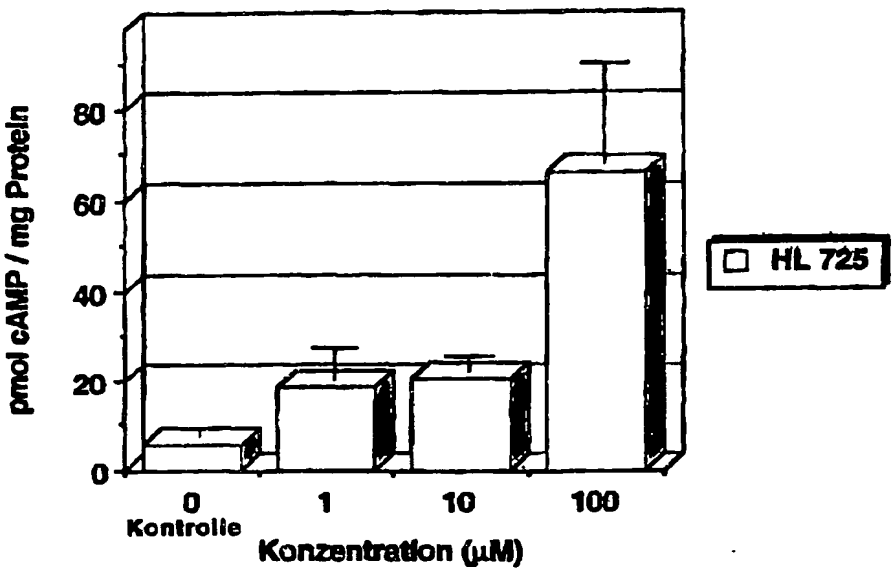

Fig. 6: Stimulating effects of different concentrations of the PDE3 inhibitor HL 725 on the tissue content of cAMP in strip preparations of isolated human detrusor musculature

Key: Kontrolle = control; Konzentration = concentration